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Non-Hodgkin Lymphoma (NHL) as a Second Neoplasm Occurring After Neuroblastoma Treatment

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As far as we know, this is the first report of a non-Hodgkin lymphoma developing after successful treatment of neuroblastoma. A boy was found to have a mediastinal T-cell lymphoma at the age of 5. He had been treated for a neuroblastoma of the left adrenal region 4 years before, when by intensive chemotherapy and radiation a complete remission of the primary tumor was achieved. The second malignancy has also been controlled without evidence of recurrence 1 year after termination of treatment. We conclude that treatment of a neuroblastoma by cytostatic drugs and radiation may lead to a non-Hodgkin lymphoma as a second malignancy. Med. Pediatr. Oncol. 30: 18–21, 1998. © 1998 Wiley-Liss, Inc.

Key words: second malignant neoplasm; childhood tumor; neuroblastoma; NHL

INTRODUCTION

Second malignancies represent late complications after successful treatment of malignant tumors, such as acute lymphoblastic leukemia, tumors of the central nervous system, retinoblastoma, Hodgkin's disease and non-Hodgkin lymphoma (NHL). Tumors of the central nervous system, acute non-lymphatic leukemia, osteosarcomas, carcinomas of the thyroid gland, and NHL dominate as second malignancies, in that order [1]. The present paper reports a very rare combination of a neuroblastoma as the primary malignancy and an NHL as the second malignancy.

CASE REPORT

At the age of 1 y 3 m the boy suffered from ataxia and a tendency to plunging. An opsoclonus was observed. The patient was examined for a tumor. By sonography and computerized tomography a tumor of 5.5 × 3.5 × 4.0 cm in size was revealed in the region of the left adrenal gland. Urinary excretion of vanillylmandelic acid and of 5-hydroxyindole acetic acid was increased. Diagnostic investigations of tumor spreading (MIBG scintigraphy, computerized tomography of the skull, examination of bone marrow smears, and X-ray examination at the thorax) ruled out a generalization of the malignant disease.

The tumor was resected from the region of the left adrenal gland by laparotomy.† Some small tumor cones had to be left behind around the aorta and the celiac trunk. Suspicious ipsi- and contralateral lymphonodi were not found. The suspicion of neuroblastoma was confirmed histologically. A typical structure with neuroblastoma cells among focal necroses and calcifications on a fibrillary background was found (Fig. 1). Here and there ganglion-like cells as a maturation phenomenon were seen. The tumor was categorized as one of grade 2 according to Hughes et al. [2]. By macroscopic and microscopic investigation the tumor capsule turned out to be incomplete, so the tumor was classified by surgery as neuroblastoma at stage 2A according to the INSS classification scheme [3]. The treatment was performed according to the scheme recommended by the Arbeitsgruppe Pädiatrische Hämatologie und Onkologie, including 3 cycles of 150 mg/m^2 of cyclophosphamide for 7 days and 35 mg/m^2 of adriamycin on the eighth day every 3 weeks, and 6 cycles of 90 mg/m^2 of cisplatinum on the first day and 100 mg/m^2 of teniposid (VM26, Bristol) on the third day every 3 weeks.

Radiation therapy of the tumor region (24.9 Gy in 18 fractions) was carried out for 6 weeks after the chemotherapy. There was no indication of residual tumor masses from sonography, scintigraphy, and catecholamine analysis at the end of treatment.

In a routine follow up chest X-ray examination 4 years after the beginning of the primary disease, a widening of

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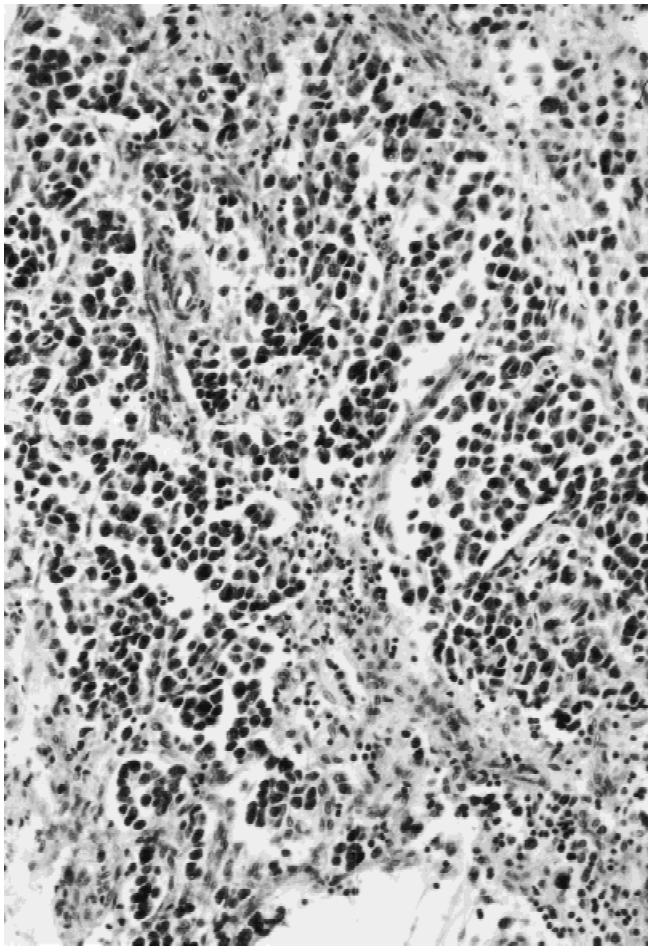

Fig. 1. Neuroblastoma with the typical cytological feature of neuroblastic tumor cells, fibrovascular septa, few rosette like formations, as well as sparse lymphocytic infiltrates. H/E, ×175.

the mediastinum was noticed. Magnetic resonance imaging identified a retrosternal mass of 10 × 8 × 5 cm in size spread out to the frontal and the central mediastinum. An enlarged lymph node was palpated in the left supraclavicular region. This lymph node and a tumor cone from the retrosternal space were extirpated. Histological examination revealed a T cell lymphoma of high-degree malignancy, suggestive of a lymphoblastic T cell lymphoma. The dense infiltrations in the mediastinal mass consisted of lymphoblastic tumor cell forms with cleaved nuclei and a sparse basophilic cytoplasm. At first glance the histological structure differed from the neuroblastoma treated years before (Fig. 2). The cells react with antibodies for CD 3 and CD 45 RO. In bone marrow smears, 12 percent of atypical blast cells were found. These findings were in conformity with stage IV NHL according to the classification by Murphy et al. [4]. Other manifestations of the lymphoma were not found by computerized tomography of the skull, analysis of the cerebrospinal fluid, sonography of the abdomen, and bone scan. There was no indication of reactivation of the primary tumor, also from the clinical test values.

NHL was treated according to the BFM-NHL-90 therapy protocol. After phase 1 of the protocol element 1, a complete remission of the mediastinal tumor and the bone marrow infiltration was detected. The remission has been sustained until now. At present, maintenance therapy is being completed. There was no evidence for a hereditary immunodeficiency either from the clinical observation or from the biochemical investigations (lymphocyte count and subfractions, immunoglobulin subclasses).

DISCUSSION AND CONCLUSIONS

After successful treatment of malignant diseases in childhood the problem of long-term complications came to the fore. Special late events are the second malignancies. Some extensive studies are concerned with this problem. On the basis of cancer registry, in five northern countries (Denmark, Finland, Iceland, Norway, Sweden)

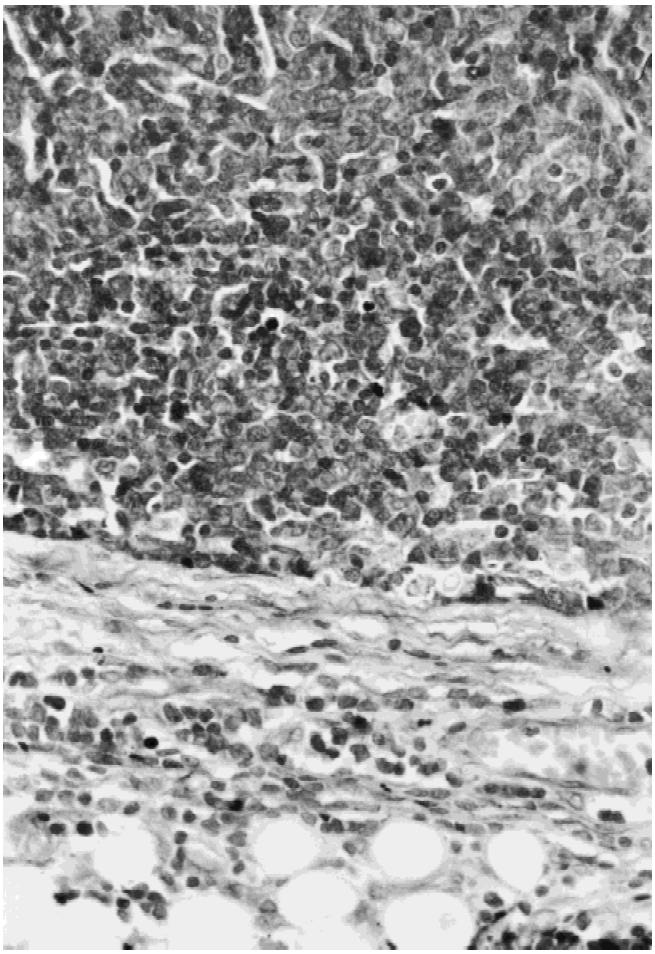

Fig. 2. Cortical and extranodal area of a lymph node with infiltrates of a lymphoblastic lymphoma. Giemsa, ×350.

altogether 30880 patients with a first malignant disease below age 20 had been enrolled for analysis [5]. During the period of 1943–1987, 247 second malignancies were seen in 238 patients. The authors compared the occurrence of second malignancies in two periods: in the forties and fifties, on one hand, and in the late seventies and eighties, on the other. The risk for a second malignancy increased from 2.6 to 6.9 percent. The primary tumors were different in both groups. But above all, different treatment modalities and increased survival are taken into account for these differences. In a British study [6], 90 second malignancies out of 10,106 three-year survivors of childhood cancer were found. This is 6 times the expected number in a normal population. The lower percentage in comparison to the former study may be a result of a lower intensity of radiotherapy and by applying less combination therapy.

In another study, the incidence of second malignancies in long-term survivors with malignant tumors in childhood is 1.0 percent within 10 years and 3.0 percent within 20 years of follow-up after treatment of the primary tumor [7]. A markedly higher rate of 8.0 percent in 20 years after successful treatment of the primary tumor was described by Hunger et al. [8]. In survivors of a first cancer in childhood the incidence of second malignancies during the first 20 years after the original diagnosis is calculated to be 3 to 12 percent in a survey by Blatt [9]. The risk for suffering from a second tumor is 10 to 20 times higher than in age-matched controls. In 1984, Tucker et al. [10] reported about 9,170 long-term survivors of childhood cancer. Of these patients, 167 showed second malignancies. A large number of second malignancies were found in patients with bilateral or familial retinoblastoma, nephroblastoma, Hodgkin's disease, and neuroblastoma.

Second malignancies may occur in an especially high frequency in connection with previous radiation, about 70 percent of all manifestations [11]. But in our patient the mediastinum was not part of the radiation field, as it was confirmed by inspection of the old radiation plans.

Other risk factors for generation of second malignancies comprise the cytostatic treatment of the primary tumor and a genetic predisposition. According to the reports of the Late Effects Study Group [12], some combinations of tumors seem to be related to underlying genetic syndromes. Our patient had received intensive chemotherapy but without a family history of an increased tumor frequency. An increased risk of second malignancies may be derived from the irradiation of the spleen or splenectomy and the resulting immunodeficiency state [13]. In our patient, the spleen was located within the radiation field supporting this hypothesis.

Within limits, the primary tumor and second malignancy exhibit a defined arrangement. Second malignancies after neuroblastoma described up to now were malignant tumors of the parotid [14], kidney cell carcinoma [15], osteogenic sarcoma [16], carcinoma and adenoma of the thyroid gland [17], acute lymphoblastic leukemia [8], and myelodysplastic syndrome and its transition to acute myelogenous leukemia [18].

In the article by Tucker et al. [10], about 790 patients with neuroblastoma, 17 second malignancies of the following origin were listed: 1 buccal cavity, 4 bone, 3 connective tissue, 1 brain, 7 thyroid gland, and 1 kidney. In addition, one patient suffered from leukemia and another from Hodgkin's disease. But Tucker et al. didn't report about non-Hodgkin lymphoma as a second tumor after neuroblastoma. NHL as a second malignancy may occur after Hodgkin's disease, acute lymphoblastic leukemia, acute myelogenous leukemia, and astrocytoma [19]. However, soft tissue sarcoma has been described as a primary tumor [20].

We describe an NHL occurring 4 years after a neuroblastoma. The histological findings are beyond any shadow of a doubt. The neuroblastoma had been resected only partially (stage 2A). But the child didn't suffer a relapse. The diagnosis of NHL was confirmed by immunological typing.

As far as we know, the combination of neuroblastoma as a primary tumor with a second NHL has not been described before, even not in a recently published review [21]. The aim of this report is to draw attention to this rare combination. It is of practical importance for patients treated for neuroblastoma, and strengthens the current recommendations that stage 2A patients with low risk factors be treated with surgery alone [22].

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